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# Changes in dual energy X-ray absorptiometry parameters in postmenopausal women with osteoporosis who received at least 12 months of denosumab treatment

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**Ethics Committee Approval**
Ethics committee approval was obtained from the Istanbul Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee. (date: 12.11.2020, decision number: KAEK 2020/113).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Denosumab is a human monoclonal antibody that binds to the receptor-activated nuclear factor kappa beta ligand (RANKL). Densosumab leads to a reduction in bone resorption by inhibiting RANKL and has been approved for treating postmenopausal osteoporosis (OP). The present study investigated real life data by evaluating the demographic data of postmenopausal patients with OP who received denosumab treatment and the changes in dual energy x-ray absorptiometry (DEXA) parameters before and after denosumab treatment.

**Methods:** This retrospective cohort study included 49 postmenopausal female patients followed in our OP outpatient clinic who were treated with 60 mg subcutaneous denosumab every six months for at least 12 months. The study retrospectively analyzed and recorded patient age, body mass index, age of menopause, fracture history, antiresorptive and/or anabolic drug treatment history, and pre- and post-denosumab T-scores in addition to L1–4, femoral neck, and total hip bone mineral densities (BMDs) on DEXA scans. The changes that occurred before and after the treatment in addition to those that occurred after the treatment based on whether previous anabolic or antiresorptive agents had been used were statistically compared.

**Results:** The L1–4 and total hip T-scores and L1–4 and total hip BMD values measured prior to denosumab treatment showed a statistically significant increase after denosumab treatment ($P < 0.001$, $P = 0.002$, $P = 0.028$, and $P = 0.002$, respectively). No statistically significant changes in the femoral neck T-score and BMD after denosumab treatment compared to that before denosumab use ($P = 0.056$ and $P = 0.138$, respectively) were found. Furthermore, no statistically significant difference between the pre- and post-denosumab DEXA parameters in the patients who used antiresorptive agents and those who did not ($P > 0.05$) was found. Additionally, pre- and post-denosumab parameters were not statistically significantly different between those who received and did not receive anabolic therapy before denosumab ($P > 0.05$).

**Conclusion:** Denosumab treatment for postmenopausal OP leads to a significant increase in lumbar and total hip T-scores and BMDs.

**Keywords:** Osteoporosis, Denosumab, Dual energy X-ray absorptiometry

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## Introduction

According to the World Health Organization, osteoporosis (OP) is defined as bone mineral density (BMD) T-scores < −2.5 standard deviations (SD) on a dual energy x-ray absorptiometry (DEXA) scan [1]. OP is a systemic skeletal disease characterized by an increase in the risk of fracture due to defects in bone microarchitecture [2]. In the FRACTURK study, the prevalence of OP in women over 50 years in Turkey was reported to be 12.5%, and the risk of hip fracture was reported to be 14.5% [3]. Osteoporotic fractures adversely affect the quality of life as OP causes pain and impairs functional capacity as a result of its negative effects on the musculoskeletal system and body posture [2]. When OP is not detected and treated properly, the economic burden of OP-related fractures on the Turkish healthcare system increases as it is on the other countries in the world [4]. Antiresorptive agents (bisphosphonates and denosumab) that act by reducing bone resorption, and teriparatide, a recombinant human parathyroid hormone with an anabolic effect, are among the main agents used today in the pharmacological treatment of OP [5]. Postmenopausal estrogen deficiency causes an increase in the exposure of receptor-activated nuclear K (RANK) B receptors on the surface of osteoclasts to RANK ligand and consequently increases bone resorption and bone loss. Denosumab is a highly potent IgG2 human monoclonal antibody that binds to the RANK ligand via a mechanism resembling the action of osteoprotegerin that prevents the ligand from binding to the RANK receptor. Denosumab is administered at a dose of 60 mg via subcutaneous injections once every six months. Studies have reported that it causes an increase in bone density by causing a decrease in osteoclastic activity and bone resorption, thereby resulting in reduction of new vertebral and nonvertebral fractures [6–8]. Our study aimed to present the demographic characteristics of postmenopausal OP patients who received regular denosumab injection for at least 12 months in our clinic in addition to real-life data that we obtained by examining the changes in DEXA measurement parameters.

## Materials and methods

The study included 49 postmenopausal female patients who were followed up in our OP outpatient clinic and administered 60 mg of denosumab subcutaneously every six months for at least 12 months. Power analysis was performed to determine the number of samples. A sample size of 34 was determined to be sufficient assuming that α was 0.05, effect size was 0.50, and power was (1 β) 0.80. G power (Version 3.1.9.6) was used for this calculation. Patients with diseases of bone metabolism, such as Paget's disease, osteomalacia, primary hyperparathyroidism, hyperthyroidism, malignancy, and malabsorption were excluded from the study. Those with T scores < −2.5 standard deviations (SDs) at three sites (total lumbar, total hip, or femoral neck) on DEXA scans were defined as having OP. This research was approved by University of Health Sciences Istanbul Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (12.11.2020/ KAEK 2020/113) and the study was conducted in accordance with the Declaration of Helsinki. The files of the patients were retrospectively reviewed. Patients' ages, body mass indices (BMIs), ages at menopausal, fracture histories, and antiresorptive and/or anabolic drug treatment histories in addition to their L1–4, femoral neck, and total hip T-scores and BMD values on DEXA scans before and after denosumab injections were recorded.

The changes that occurred before and after the treatment and the changes that occurred after the treatment based on whether there had been an anabolic or antiresorptive agent used prior to the treatment were compared statistically.

**Statistical analysis**

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis of the findings obtained in the study. While evaluating the study data, the conformity of the parameters to the normal distribution was evaluated using the Shapiro–Wilk test. Along with the descriptive statistics (mean, SD, and frequency) used in the data analysis, Student's t-test was also used for comparing two groups with normally distributed quantitative data. A paired samples t-test was used for the before/after comparisons of normally distributed quantitative data. Moreover, $P < 0.05$ was considered as statistically significant.

## Results

The study was conducted with 49 postmenopausal women aged 48 to 92 years who were followed up in our OP outpatient clinic between 2014 and 2020. The mean age of the cases was 68.63 (8.27) years, and the mean BMI was 26.99 (4.76) kg/m$^2$. Menopausal ages ranged from 27 to 62 years with a mean of 47.22 (8.07) years. The months in which control DEXA was performed after denosumab ranged from the 12$^{th}$ to the 54$^{th}$ month with a mean of 23.8 (12.3) months. A total of 32.7% of the patients had at least one vertebral compression fracture, 4.1% had femur fractures, 24.5% had vertebral and non-femoral fractures, 93.9% had a history of antiresorptive drug use before denosumab, and 20.4% had a history of anabolic drug use before denosumab. Although 65.3% of these patients continued their treatment again with denosumab after the initial denosumab administration, 26.6% continued with antiresorptive treatment instead. The type of treatment that was continued after denosumab administration is unknown in 8.2% of the patient population (Table 1).

Table 1: Demographic data and clinical characteristics of the cases

| | | Min/Max | Mean /SD |
|---|---|---|---|
| Age | | 48/92 | 68.63 /8.27 |
| BMI | | 16.8/36.5 | 26.99 /4.76 |
| Menopausal age | | 27/62 | 47.22 /8.07 |
| Months during which control DEXA was performed after denosumab | | 12/54 | 23.85 /12.3 |
| | | n | % |
| Vertebral compression | Yes | 16 | 32.7 |
| | No | 33 | 67.3 |
| Femur fracture | Yes | 2 | 4.1 |
| | No | 47 | 95.9 |
| Other fractures | Yes | 12 | 24.5 |
| | No | 37 | 75.5 |
| Antiresorptive use | Yes | 46 | 93.9 |
| before denosumab | No | 3 | 6.1 |
| History of anabolic treatment | Yes | 10 | 20.4 |
| before denosumab | No | 39 | 79.6 |
| Post-denosumab treatment | Denosumab continued | 32 | 65.3 |
| | Antiresorptive therapy | 13 | 26.5 |
| | Unknown | 4 | 8.2 |

Min: minimum, Max: maximum, SD: standard deviation, BMI: body mass index, DEXA: dual energy X-ray absorptiometry

The increase in the T-score at L1–4 after denosumab administration versus the scores before denosumab administration was found to be statistically significant ($P < 0.001$ versus $P < 0.01$). Compared to the values prior to denosumab administration, the increase in the BMD values at L1–4 after denosumab was also statistically significant ($P = 0.028$). No statistically significant changes in T-scores and BMDs at the femoral neck were observed after denosumab administration compared with the values before administration ($P = 0.056$ and $P = 0.138$, respectively). The increase in total hip T-scores after starting denosumab treatment was found to be statistically significant compared to the scores before denosumab administration ($P = 0.002$). Moreover, the increase in the total hip BMD values after denosumab administration was found to be statistically significant compared to the values before denosumab administration ($P = 0.002$) as shown in Table 2.

Table 2: Comparison of bone mineral density (BMD) measurements of the cases before and after denosumab treatment

| | | Before denosumab | | After denosumab | | *P*-value |
|---|---|---|---|---|---|---|
| | | Min/Max | Mean/SD | Min/Max | Mean/SD | |
| L1–4 | T score | −3.8/−0.8 | −2.6/0.66 | −3.7/−0.1 | –2.26/0.77 | <0.001* |
| | BMD | 0.68/1.05 | 0.82/0.08 | 0.6/2.08 | 0.89/0.21 | 0.028* |
| Femoral neck | T score | −3/−0.6 | −1.99/0.63 | −3.2/0 | –1.87/0.62 | 0.056 |
| | BMD | 0.51/0.87 | 0.71/0.08 | 0.56/0.95 | 0.72/0.08 | 0.138 |
| Total hip | T score | −3.1/−0.5 | –1.79/0.68 | −3.1/−0.5 | –1.71/0.65 | 0.002* |
| | BMD | 0.6/0.91 | 0.76/0.09 | 0.61/0.91 | 0.77/0.08 | 0.002* |

BMD: bone mineral density, Min: minimum, Max: maximum, SD: standard deviation, Paired samples t test *$P < 0.05$

The pre- and post-denosumab L1–4 T scores, L1–4 BMDs, total hip T-scores and total hip BMDs were not statistically significantly different between patients who used antiresorptive agents and those who did not ($P = 0.427$, $P = 0.765$, $P = 0.110$, and $P = 0.11$, respectively). The femoral neck pre-denosumab T-scores and BMD values in those using antiresorptive agents before denosumab were found to be statistically significantly higher than those who did not use antiresorptive agents before denosumab treatment ($P = 0.013$ and $P = 0.020$ respectively); however, no significant differences in the same parameters after denosumab administration ($P = 0.081$ and $P = 0.093$ respectively) were noted (Table 3).

The pre- and post-denosumab L1–4 T scores ($P = 0.403$ and $P = 0.916$, respectively) and BMDs ($P = 0.251$ and $P = 0.473$, respectively), femoral neck T scores ($P = 0.504$ and $P = 0.600$, respectively), and BMDs ($P = 0.327$ and $P = 0.424$, respectively) did show pre- and post-treatment statistical differences. However, total hip T scores ($P = 0.668$ and $P = 0.684$, respectively) and corresponding BMDs ($P = 0.582$ and $P = 0.474$, respectively) did not demonstrate statistically significant differences between the patients who received anabolic agents before denosumab and those who did not (Table 3).

Table 3: Comparison of the BMD values after denosumab treatment based on the use of antiresorptive or anabolic treatment before denosumab

| | | | Antiresorptive use before denosumab | | | Anabolic therapy use before denosumab | | |
|---|---|---|---|---|---|---|---|---|
| | | | Yes Mean/SD | No Mean/SD | *P*-value | Yes Mean/SD | No Mean/SD | *P*-value |
| L1–4 | T score | Before denosumab | −2.62/0.67 | −2.3/0.35 | 0.427 | −2.75/0.65 | −2.55/0.66 | 0.403 |
| | | After denosumab | −2.27/0.8 | −2.13/0.38 | 0.765 | −2.29/0.95 | −2.26/0.74 | 0.916 |
| | BMD | Before denosumab | 0.82/0.08 | 0.87/0.04 | 0.332 | 0.8/0.07 | 0.83/0.08 | 0.251 |
| | | After denosumab | 0.89/0.22 | 0.89/0.05 | 0.988 | 0.97/0.43 | 0.86/0.1 | 0.473 |
| Femoral neck | T score | Before denosumab | −1.92/0.6 | −2.83/0.21 | 0.013* | −2.13/0.58 | −1.95/0.65 | 0.504 |
| | | After denosumab | −1.82/0.6 | −2.47/0.47 | 0.081 | −1.99/0.39 | −1.85/0.66 | 0.600 |
| | BMD | Before denosumab | 0.72/0.08 | 0.61/0.03 | 0.020* | 0.68/0.09 | 0.72/0.08 | 0.327 |
| | | After denosumab | 0.73/0.07 | 0.65/0.06 | 0.093 | 0.7/0.05 | 0.73/0.08 | 0.424 |
| Total hip | T score | Before denosumab | −1.74/0.68 | −2.4/0.44 | 0.110 | −1.89/0.85 | −1.77/0.64 | 0.668 |
| | | After denosumab | −1.66/0.64 | −2.27/0.55 | 0.121 | −1.8/0.71 | −1.69/0.65 | 0.684 |
| | BMD | Before denosumab | 0.77/0.09 | 0.69/0.06 | 0.131 | 0.75/0.11 | 0.77/0.08 | 0.582 |
| | | After denosumab | 0.78/0.08 | 0.71/0.07 | 0.122 | 0.75/0.08 | 0.78/0.08 | 0.474 |

BMD: bone mineral density, SD: standard deviation, Students t test *$P < 0.05$

## Discussion

Initiating pharmacological treatment in OP patients who present an increase in risk of fractures is recommended. Although bisphosphonates have been the first-line treatment in the treatment algorithm for many years, denosumab treatment is among the first-line treatment options as an alternative to bisphosphonates [9]. Especially when compared to oral bisphosphonates, denosumab is a treatment with higher patient compliance [10, 11]. In their retrospective study, Cairoli et al. [12] compared findings in patients who received postmenopausal OP treatment with denosumab with those in patients who received postmenopausal OP treatment with oral bisphosphonates. At the end of 24 months, those who received denosumab treatment were found to have a higher reduction in alkaline phosphatase, higher increase in BMD, and lower incidence of new fractures and treatment unresponsiveness.

In our study, the mean age, BMI, and mean menopausal age of our cases were found to be consistent with those reported in literature [8]. According to the short- and long-term findings of the FREEDOM study, denosumab treatment leads to suppression of osteoclastic activity, slowing down of the bone remodeling process, and an increase in the total lumbar, total femur, and femoral neck BMDs in proportion to the duration of use, thus leading to a reduction in the risk of new vertebral fractures by 68%, nonvertebral fractures by 20%, and hip fractures by 40% [6, 8, 13]. The results from a transiliac biopsy performed in 41 patients who received denosumab treatment for five years showed that the bone quality of the patients was natural, and their bone turnover was low. This result, in line with literature, supports the effectiveness of denosumab treatment in producing an increase in BMD and reduction in the incidence of fractures [14]. Another study reported that changes in assessment and follow-up BMD values and T-scores on DEXA scans were strong indicators of fracture risk in cases undergoing denosumab treatment [15]. In our study, the average scan time after the treatment was approximately 23 months, and although the total lumbar and total hip BMDs and T-scores increased in our cases after denosumab treatment in line with results reported in the

literature, no increase was observed in femoral neck BMDs and T-scores, a result that is in contrast with that observed in literature. This finding could be explained by the fact that the treatment and follow-up periods of the cases in similar studies in literature were longer than those of our cases.

Several randomized controlled studies have evaluated the safety and the efficacy of denosumab and have found it to be generally well tolerated; it has also been reported that the frequency of possible side-effects, such as cancer, cardiovascular diseases, delayed fracture healing, hypocalcemia, development of opportunistic infections, neutralizing antibody formation, atypical femur fracture, and/or osteonecrosis of the jaw, did not increase compared to placebo. [6, 8, 13]. In a study evaluating the effects of denosumab treatment on fracture healing, denosumab was administered to patients with nonvertebral fractures within six weeks before and after the fracture, and no delay in fracture healing nor increased nonunion was observed compared to the placebo group [16]. However, it has been reported that the frequency of eczema increased compared to placebo [6].

Bisphosphonates accumulate in bone, whereas denosumab does not. Denosumab causes a rapid decrease in total lumbar, total hip, and femoral neck BMDs and a rapid increase in bone turnover markers in accordance with its mechanism of action, in case of treatment discontinuation [7, 17–19]. For this reason, re-examining patients receiving denosumab treatment for any fracture risk after five years and extending the treatment to 10 years in those with high fracture risk or switching to an alternative treatment, such as bisphosphonates, is recommended. In patients with low fracture risk, if cessation of denosumab treatment is desirable, discontinuing such treatment and developing an alternative treatment plan to manage the rapid BMD decrease and the potential vertebral fracture risk increase is recommended [19, 20]. Although the mean evaluation period of the cases in our study was two years, which is shorter than that of the existing studies, 65.3% of our cases continued with denosumab, 26.5% with antiresorptive agents, and 8.2% of the cases could not be followed.

Bisphosphonates are contraindicated in some cases, especially those in which the glomerular filtration rate is as low as <30 ml/min. On the other hand, although denosumab may be preferred in OP cases with chronic renal failure, exercising caution in terms of the risk of hypocalcemia is recommended [21, 22]. A retrospective study by Fraser et al. examined the changes in BMD after denosumab treatment administered to patients who had previously received bisphosphonate therapy and the effect of chronic renal failure on this change. According to the results reported in this study, denosumab treatment after bisphosphonates led to an increase in total lumbar, total hip, and femoral neck BMDs, whereas denosumab response was reported to be lower in terms of femoral neck BMD in proportion to the elevation in serum parathormone concentrations caused by chronic renal failure [23]. As the prevalence and duration of denosumab use in the treatment of OP increased, transitions between other treatments for OP and denosumab has gained further importance. In our study, the treatments that the cases received before denosumab were also evaluated, and it was seen that most cases, namely, 93.9% received antiresorptive treatment before starting denosumab. Consistent with the current study, a similar increase was observed in the total hip and total lumbar BMDs, except for the femoral neck BMD and T-scores in another study. In our study, pre- and post-denosumab BMD values and T-scores on DEXA scans were compared in patients with and without a history of antiresorptive treatment. Although only the femoral neck pre-denosumab BMD and T-scores were statistically higher in patients with a history of bisphosphonate treatment, no difference between the groups after treatment was observed. Again, no difference between those with and without a history of bisphosphonate use in terms of the total hip and total lumbar BMDs and T-scores before and after starting denosumab was noted. However, the results provide insufficient information as the number of patients who did not receive bisphosphonate therapy was very small. Furthermore, in our study, whether the cases received anabolic treatment history before the treatment or not was evaluated, but no significant difference was observed between the groups. According to the results of a randomized controlled trial that evaluated the outcome of the transition between denosumab and teriparatide treatments, BMD values continued to increase when switching from teriparatide to denosumab treatment in patients receiving postmenopausal OP treatment, whereas switching from denosumab to teriparatide treatment resulted in a progressive or temporary decrease in BMD [24].

**Limitations**

As our study was retrospectively conducted and did not have a control group, our primary limitations are not fully revealing the side-effects of the cases that received treatment, the short follow-up durations of the cases, and the small number of cases herein. However, it is notable that our study presents real-life data concerning denosumab use in postmenopausal OP treatment in Turkey. In Turkey, the need for randomized controlled clinical studies with longer follow-up periods and larger patient groups exists with the aim of demonstrating the efficacy of denosumab treatment and how the efficacy of treatment is affected in transitions between denosumab and other treatments.

**Conclusion**

Denosumab treatment may be an effective treatment option for postmenopausal OP as it leads to an increase in BMD values and T-scores on DEXA scans. As denosumab is one of the first-line treatments for OP, treatment transitions between denosumab and other antiresorptive or anabolic agents have also gained importance. This study provides real-life data addressing denosumab therapy, which has an important place in the treatment of osteoporosis.

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